

Original article

Anterior segment optical coherence tomography changes with introduction and discontinuation of tamsulosin

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Abstract

Purpose: The aim of this study was to quantify changes and reversibility in pupil dilation and iris dilator muscle region thickness associated with introduction and subsequent discontinuation of tamsulosin in patients naïve to this drug with the aid of an anterior OCT system.

Methods: The study was carried out on 7 patients (14 eyes) naïve to tamsulosin and with benign prostatic hypertrophy (BPH). Measurements taken by Vistante OCT were done pre- and post-dilation of the following: pupil size, iris dilator muscle region (DMR) thickness, sphincter muscle region (SMR) thickness, and anterior chamber depth. These measurement were taken at Day 0 (tamsulosin naïve), Day 30 (after one month of tamsulosin, the treatment period) and day 60 (after one month of no tamsulosin, the discontinuation period).

Results: Post-dilation pupil diameter significantly increased during the discontinuation period ($P = 0.047$). Iris DMR thickness measurements post-dilation significantly decreased during treatment ($P = 0.00044$), discontinuation (0.00011), and combined periods ($P = 0.000050$). Anterior chamber depth measurements in post-dilation were significantly decreased during treatment ($P = 0.0016$), discontinuation ($P = 0.017$), and combined periods ($P = 0.00022$).

Conclusion: Tamsulosin discontinuation effectively increases dilated pupil size, a measure that has been inversely linked to IFIS incidence pre-operatively. Decreased DMR thickness in this short term likely illustrates changes aside from atrophy, such as vascular changes. Decreased anterior chamber depths suggest aqueous humor production is decreased as well.

Keywords: Intraoperative floppy iris syndrome, Cataract surgery, Optical coherence tomography, Flomax, Tamsulosin, Benign prostatic hypertrophy

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Introduction

Benign prostatic hyperplasia (BPH) is a common condition affecting 2.7% of men aged 45–49 years and as high as 24% for men over 80 years old.¹ Pharmacological treatment of BPH involves the use of α_1 -adrenoreceptor antagonists,

such as tamsulosin. This drug is now known to many ophthalmologists through its association with iris changes that complicate cataract surgery.² These changes have been coined as intraoperative floppy iris syndrome (IFIS) by Chang and Campbell.³

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In tamsulosin patients, a decreased preoperative dilated pupil diameter is associated with increased risk of IFIS.⁴ Chang hypothesized that this was caused by a blockage of α_{1A} adrenoreceptors (α_{1A} -AR) in the iris dilator muscle. Tamsulosin users have been observed to have decreased dilated pupil diameters compared to control groups.^{5,6} Pupil diameter decreases have also been observed with tamsulosin introduced to tamsulosin-naïve patients.⁷

In addition to pupil diameter changes, it is hypothesized that α_{1A} -adrenoreceptor antagonists lead to loss of iris dilator muscle tone and disuse atrophy due to chronic blockage of the α_{1A} receptor on the muscle.^{3,8} This could explain both the flaccid characteristic of the tissue as found during cataract surgery and the occurrence of IFIS despite discontinued usage before surgery.⁹ In support of atrophy, it has been found by optic coherence tomography, tamsulosin users have decreased iris thicknesses in the dilator muscle region.⁶

The aim of this study was to quantify changes and reversibility in pupil dilation and iris dilator muscle region thickness associated with an introduction and subsequent discontinuation of tamsulosin in patients naïve to this drug with the aid of an anterior OCT system. A small cohort of patients on tamsulosin was followed longitudinally to see whether any changes that may occur are reversible. To date, no other study has examined the anterior chamber morphology of tamsulosin naïve patients with a discontinuation period.

Patients and methods

Patients were recruited from the Urology Clinic and tested at the Eye Clinic in Toronto Western Hospital. Testing included 7 patients and 14 eyes, all of men in age range of 60–80 years old. There is no significant post void residual or urinary retention in any of the selected patients. All patients received an explanation of the risks involved and provided informed consent. The inclusion criteria included any diagnosis of BPH, if Tamsulosin deemed clinically necessary and no previous exposure to α_1 -adrenoreceptor antagonist. Exclusion criteria were eye drop usage besides artificial tears (i.e. mydriatics or α_1 -AR agonist), previous angle closure glaucoma, Pseudoexfoliation syndrome, previous ocular surgery (i.e. laser iridoplasty, cataract surgery), Horner's syndrome, ocular trauma and uveitis.

The study was carried out on 7 patients (14 eyes) with BPH and naïve to tamsulosin usage. One patient was diabetic. Anterior chamber OCT images of participants' eyes were

taken at 3 different points in time over a 2 month duration, prior to tamsulosin, at the end of 30 day tamsulosin course, and another 30 days after completion of therapy. Measurements were made by OCT Visante software (Carl Zeiss Co.) at each of the three points in time, before and after dilation of each eye with Diophenyl-T eyedrops (Phenylephrine Hydrochloride 5%; Tropicamide 0.8%).

Measurements of interest were as follows: pupil size, iris dilator muscle region (DMR) thickness, iris sphincter muscle region (SMR) thickness, and anterior chamber depth. These were measured from the OCT images through use of the anterior chamber OCT (Fig. 1).

All tests were performed in the same clinic with the same instruments during the course of the study. Patients were examined and evaluated for a complete eye history before starting the study including in clinic pretest slit lamp biomicroscopy examination for the evaluation of anterior chamber, pupils, diameter, and refractivity. Additionally, OCT imaging measurements of pupil size measured between papillary margins, iris dilator muscle region (DMR) measured halfway between the scleral spur and pupil margin and iris sphincter muscle region (SMR) measured within anterior 0.75 mm from pupil margin at the thickest and thinnest aspects were recorded. The anterior chamber depth (ASD) measured from the anterior border of lens to the posterior border of cornea was also recorded. None of the patients experienced any urinary symptoms or complications. There were no patients lost to follow-up during the study.

Statistical analysis

Measurements for each eye at the start and end of the treatment, discontinuation, or combined period were analyzed using SPSS[®] version 20.0 (IBM Inc., Chicago, Illinois, USA). Shapiro-Wilk test was used to test for normality and the data were not normally distributed; hence, Friedman test was used to compare the paired data. Each eye was treated as an independent sample. The null hypothesis was set as no difference between the start and end of a period for all measures of pupil diameter, iris thicknesses, and anterior chamber depth. Significance was considered as $P < 0.05$.

Results

The post-dilation pupil diameter was found to be significantly increased during the discontinuation period

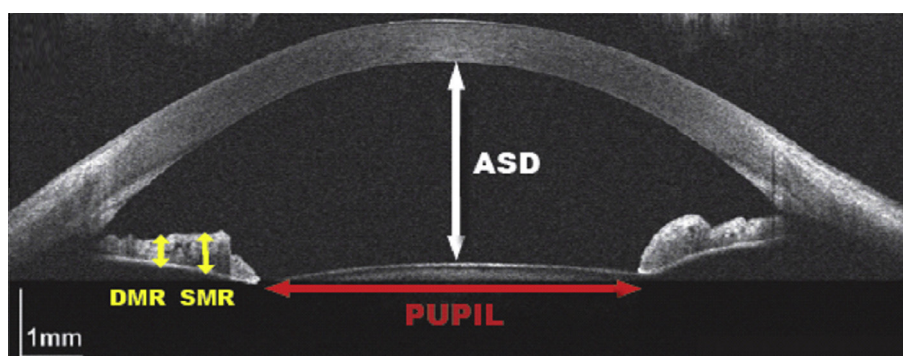


Figure 1. An example of anterior chamber imaging by Carl Zeiss Meditec's VisanteTM OCT system demonstrating standardized positions of measurement. This imaging allows accurate measurement of pupil size, iris dilator muscle region (DMR) thickness, iris sphincter muscle region (SMR) thickness, and anterior chamber depth (ASD).

Table 1. Pupil sizes expressed as mean \pm standard deviation in mm.

	Stage of tamsulosin usage			Treatment period (Day–30)		Discontinuation period (Day–60)		Combined period (Day–60)	
	Day 0 (before tamsulosin exposure)	Day 30 (after 1 month of exposure)	Day 60 (after 1 month of discontinuation)	Difference between start and end	P-value	Difference between start and end	P-value	Difference between start and end	P-value
Pupil diameter change with dilation	2.80 \pm 0.70	2.81 \pm 0.79	3.12 \pm 0.62	0.02 \pm 0.80	0.92	0.31 \pm 0.87	0.24	0.32 \pm 0.73	0.17
Pre-dilation pupil diameter	3.21 \pm 0.64	2.96 \pm 0.56	2.98 \pm 0.46	–0.25 \pm 0.46	0.064	0.02 \pm 0.56	0.92	–0.23 \pm 0.49	0.12
Post-dilation pupil diameter	5.93 \pm 0.56	5.75 \pm 0.81	6.07 \pm 0.63	–0.18 \pm 0.59	0.33	0.32 \pm 0.49	0.047	0.14 \pm 0.39	0.26

Table 2. Dilator muscle region thicknesses expressed as mean \pm standard deviation in mm.

	Stage of tamsulosin usage			Treatment period (Day 0–30)		Discontinuation period (Day 30–60)		Combined period (Day 0–60)	
	Day 0 (before tamsulosin exposure)	Day 30 (after 1 month of exposure)	Day 60 (after 1 month of discontinuation)	Difference between start and end	P-value	Difference between start and end	P-value	Difference between start and end	P-value
DMR pre-dilation thickness	0.51 \pm 0.053	0.48 \pm 0.043	0.46 \pm 0.041	–0.030 \pm 0.023	0.00032	–0.019 \pm 0.018	0.0015	–0.049 \pm 0.031	0.000051
DMR post-dilation thickness	0.63 \pm 0.054	0.59 \pm 0.061	0.57 \pm 0.057	–0.041 \pm 0.032	0.00044	–0.013 \pm 0.0090	0.00011	–0.054 \pm 0.034	0.000050

Table 3. Ratio value between dilator muscle region and sphincter muscle region expressed as mean \pm standard deviation.

	Stage of tamsulosin usage			Treatment period (Day 0–30)		Discontinuation period (Day 30–60)		Combined period (Day 0–60)	
	Day 0 (before tamsulosin exposure)	Day 30 (after 1 month of exposure)	Day 60 (after 1 month of discontinuation)	Difference between start and end	P-value	Difference between start and end	P-value	Difference between start and end	P-value
Pre-dilation DMR/SMR ratio	0.92 \pm 0.18	0.88 \pm 0.15	0.85 \pm 0.13	−0.047 \pm 0.049	0.0028	−0.029 \pm 0.044	0.024	−0.076 \pm 0.066	0.00080
Post-dilation DMR/SMR ratio	1.1 \pm 0.14	1.0 \pm 0.13	1.0 \pm 0.11	−0.076 \pm 0.066	0.0020	−0.023 \pm 0.022	0.0042	−0.099 \pm 0.073	0.00061

Table 4. Thickest and thinnest sphincter muscle region thicknesses expressed as mean \pm standard deviation in mm.

	Stage of tamsulosin usage			Treatment period (Day 0–30)		Discontinuation period (Day 30–60)		Combined period (Day 0–60)	
	Day 0 (before tamsulosin exposure)	Day 30 (after 1 month of exposure)	Day 60 (after 1 month of discontinuation)	Difference Between Start and End	P-value	Difference between start and end	P-value	Difference between start and end	P-value
Thickest pre-dilation SMR	0.56 \pm 0.10	0.56 \pm 0.076	0.56 \pm 0.077	0.0036 \pm 0.040	0.71	−0.00071 \pm 0.0027	0.32	0.0029 \pm 0.040	0.80
Thickest post-dilation SMR	0.58 \pm 0.064	0.58 \pm 0.068	0.58 \pm 0.063	−0.0025 \pm 0.011	0.44	−0.0017 \pm 0.0083	0.48	−0.0042 \pm 0.012	0.21
Thinnest pre-dilation SMR	0.31 \pm 0.029	0.31 \pm 0.022	0.31 \pm 0.023	0.00071 \pm 0.011	0.83	−0.00071 \pm 0.0062	0.71	0.0 \pm 0.013	0.998
Thinnest post-dilation SMR	0.31 \pm 0.026	0.30 \pm 0.024	0.31 \pm 0.022	−0.0058 \pm 0.0090	0.047	0.0042 \pm 0.0090	0.13	−0.0017 \pm 0.0072	0.43

($+0.32 \pm 0.49$ mm, $P = 0.047$). Other changes were not statistically significant. See Table 1 for the pupil diameter findings.

Iris DMR thicknesses at pre-dilation and post-dilation were significantly decreased during treatment, discontinuation, and combined periods. Changes in pre-dilation measurements during these periods, respectively, were -0.030 ± 0.023 mm ($P = 0.00032$), -0.019 ± 0.018 mm, $P = 0.0015$ and -0.049 ± 0.031 mm, $P = 0.000044$. Changes for post-dilation measurements during these periods, respectively, were -0.041 ± 0.032 mm ($P = 0.00044$), -0.013 ± 0.0090 mm ($P = 0.00011$), and -0.054 ± 0.034 mm ($P = 0.000050$). See Table 2 for iris dilator muscle region thickness findings.

DMR/SMR ratios at pre-dilation and post-dilation were significantly decreased during treatment, discontinuation, and combined periods. Changes in pre-dilation measurements during these periods, respectively, were -0.047 ± 0.049 ($P = 0.0028$), -0.029 ± 0.044 ($P = 0.024$) and -0.076 ± 0.066 ($P = 0.00080$). Changes in post-dilation measurements during these periods, respectively, were -0.076 ± 0.066 ($P = 0.0020$), -0.023 ± 0.022 ($P = 0.00042$), and -0.099 ± 0.073 ($P = 0.000061$). See Table 3 for ratios of DMR to SMR for each eye.

There was no significant change in either thickest or thinnest SMR measurement at pre- or post-dilation during any period of the study. See Table 4 for SMR thickness values.

Post-dilation anterior chamber depth measurements were significantly decreased during treatment, discontinuation, and combined periods. Changes in post-dilation measurements during these periods, respectively, were -0.023 ± 0.019 ($P = 0.0017$), -0.026 ± 0.033 ($P = 0.016$), and -0.049 ± 0.032 ($P = 0.00022$). See Table 5 for anterior chamber depth values.

Discussion

The post-dilation pupil diameter was found to increase during the discontinuation period. This may be due to a decreased concentration of tamsulosin, which has a half-life of 14 h and is a competitive antagonist.¹⁰ In a study by Parssinen, tamsulosin concentrations in aqueous humor were below quantification in one patient after a 21 day pause of therapy.¹¹ Our findings suggest that pupil size changes secondary to tamsulosin may be reversible in the short-term.

A second contributing factor toward greater pupil diameter is upregulation of adrenergic receptors in response to drug exposure. This idea was proposed in a study with rats exposed to 1 month of tamsulosin treatment followed by 1 month of washout.¹² It theorized the maintenance of upregulated α_{1a} -AR washout in order to explain dilated pupil diameters of rats that were, albeit statistically insignificant, larger at washout than baseline when dilated with an alpha agonist but not with another mydriatic agent. The results in our study are similar. In an analysis by Panagis, an eye of significantly longer exposure did not show upregulation on immunoreactive histopathologic analysis.¹³

Clinically, the possibility of reversibility of dilated pupil diameter with discontinuation of tamsulosin is important. Decreased diameters have been shown to have both an increase in severity and frequency of IFIS.^{4,14}

We found that DMR thickness decreased during treatment and, surprisingly, also during discontinuation of the

Table 5. Anterior chamber depth expressed as mean \pm standard deviation in mm.

	Stage of tamsulosin usage			Treatment period (Day 0–30)		Discontinuation period (Day 30–60)		Combined period (Day 0–60)	
	Day 0 (before tamsulosin exposure)	Day 30 (after 1 month of exposure)	Day 60 (after 1 month of discontinuation)	Difference between start and end	P-value	Difference between start and end	P-value	Difference between start and end	P-value
Pre-dilation ACD	2.67 ± 0.40	2.66 ± 0.39	2.66 ± 0.39	-0.00079 ± 0.027	0.31	0.0014 ± 0.025	0.87	-0.0064 ± 0.039	0.59
Post-dilation ACD	2.78 ± 0.38	2.76 ± 0.37	2.73 ± 0.39	-0.023 ± 0.019	0.0017	-0.026 ± 0.033	0.016	-0.049 ± 0.032	0.00022

treatment. Decreased thickness during discontinuation period may be explained by the effect of the residual levels of the drug. Similar to this study, Prata found decreased DMR and DMR/SMR ratio values on OCT imaging of eyes exposed to tamsulosin for an average 28.2 months.⁶ Iris dilator muscle atrophy is also a plausible explanation to account for some of the thickness decreases in the Prata study.

Histologically, the muscular layer is a small portion of the iris thickness and its atrophy could not solely account for decreased thickness in this study. Nonetheless, atrophy within iris dilator muscle has been found in eyes exposed to longer durations of tamsulosin.⁸ There are likely to be other components of the iris, such as the vasculature, which may account for the iris thickness changes in this study. Much of the iris structure is vascularized stroma composed of arterioles that do not bifurcate or anastomose.¹⁵ Immunohistochemical analysis by Panagis showed markedly decreased α_{1A} -AR immunoreactivity of the arteriolar lumen of IFIS iris tissue compared to non-IFIS tissue.¹³ In contradiction to this, a study of rat iris arterioles showed a pharmacological response of these blood vessels consistent with the activation of α_{1B} -AR, but not α_{1A} -AR.¹⁶ However, this may be accounted for by difference between species. Vasculature changes may be dynamic as opposed to morphological as Panagis did not show iris morphological changes in IFIS eyes compared to control. A similar observation was found in a cadaveric study by Santaella that found no significant difference in iris stroma.⁸

Despite lack of documented effect of an α_{1A} -AR on iris arteriolar structure or function, Panagis proposed that iris vasculature provides the structural support for the iris and has the ability to coil and uncoil to allow for iris dilation.¹³ The loss of this arteriole coiling ability would decrease iris dilation.¹³ This would be consistent with our findings if this proposed coiling is structurally thinner. Vasoconstriction is also a possible explanation for iris thickness changes but α_1 -AR antagonism by prazosin has been observed to block vasoconstriction in rat iris arterioles.¹⁶ The effect of a selective α_{1A} -AR antagonist such as tamsulosin on vascular function is not known. Furthermore, vascular dysfunction may also lead to iris dilator muscle atrophy due to a deterioration of arteriolar nutritive functions.

The findings of decreased anterior chamber depth by OCT were found only in dilated pupils. This may occur as a result of decreased aqueous humor. Alpha-1 ARs play a role in aqueous humor dynamics. Specific agonists for α_1 -ARs increase intraocular pressure while specific antagonists decrease intraocular pressure.¹⁷ A study by Zhan found that bunazosin (an α_1 -AR antagonist) treatment significantly decreased intraocular pressure with increased uveoscleral outflow in rabbits.¹⁸ A study by Krupin found prazosin (an α_1 -AR antagonist) decreased aqueous humor production but did not change outflow.¹⁹ In another study of prazosin, Chiou observed 55% reduction in aqueous humor production and 25% reduction in aqueous humor outflow during a 3 h period in the cat eye model.²⁰ It would thus be expected that another α_1 -AR antagonist such as tamsulosin would also decrease aqueous humor volumes. A study by Suzuki found that the mRNA levels of different α_1 -AR subtypes in the ciliary body were 99.2% comprised of the α_{1A} -AR subtypes.¹⁷ The selectivity of tamsulosin for the α_{1A} -AR subtype and its mRNA predominance in the ciliary body provides a physiological

pathway for decreased aqueous humor as made evident in our study by decreased anterior chamber depth.¹⁰ Our study suggests that tamsulosin affects aqueous humor production and may provide benefit to glaucoma therapy. Tamsulosin's effect on glaucoma has not been studied to our knowledge and provides an avenue for further research into its effects on anterior chamber depth, aqueous humor production and outflow, and intraocular pressure.

In conclusion, the findings of this study suggest pupil diameter changes are reversible and suggest possible reversibility of IFIS as well for short-term users. It demonstrates iris thickness effects but not the significance of this in relation to IFIS incidence remains to be determined. Our study demonstrates novel findings of an effect of tamsulosin on anterior chamber depth. This is likely through aqueous humor changes and is of relevance to glaucoma treatment. The findings of this study are limited by the small cohort size as well as a lack of placebo group to compare findings. Furthermore, the treatment period is short and conclusions cannot be extrapolated to long-term usage. Although the discontinuation follow-up period was thirty days, findings such as decreased DMR may normalize given longer follow-up. Directions for future research include anterior chamber depth, aqueous humor and intraocular pressure changes with tamsulosin in the context of glaucoma treatment effects. Furthermore, it remains to be determined whether or not discontinuing tamsulosin in short-term users has an effect on IFIS incidence and severity.

Conflict of interest

None.

Financial disclosure

No author has a financial or proprietary interest in any material or method mentioned in study.

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